was filed. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. In re Borkowski, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). See also M.P.E.P. § 2164.02.

A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

The specification teaches packaging cell lines engineered to express lentivirus proteins, including HIV proteins, necessary for virus particle formation (gagpol proteins), without containing nucleic acid sequences from lentivirus or HIV accessory proteins (tat, vif, vpr, vpu, nef and rev proteins and RRE) or constitutive transport elements CTEs) (see, e.g., page 9, lines 17-21; and page 10, lines 13-17). The specification teaches that these cell lines can be produced using a three plasmid expression system. In particular, the specification teaches that cell lines engineered to express lentivirus-derived, including HIV-derived, retroviral particles having no viral accessory proteins can be produced by co-transfecting mammalian host cells with (1) a first plasmid or retroviral nucleotide sequence (packaging construct) comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g., HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs; (2) a second plasmid or retroviral nucleotide sequence (envelope coding plasmid) comprising a DNA sequence which encodes a heterologous envelope protein; and (3) a third plasmid or retroviral nucleotide sequence (transfer vector) comprising a DNA sequence of interest and lentivirus or HIV cis-acting sequences required for packaging, reverse transcription and integration (see, e.g., page 4, lines 19-27; page 5, lines 4-12; page 9, lines 17-21; page 10, lines 13-17; and page 12, line 22 to page 13, line 2).

The specification also teaches that lentivirus-derived, including HIV-derived, retroviral particles having no viral accessory proteins can be generated using a three plasmid expression

system. In particular, the specification teaches that lentivirus-derived, including HIV-derived, retroviral particles having no viral accessory proteins can be generated by co-transfecting mammalian host cells with (a) a packaging construct comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g., HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs; (b) a envelope encoding plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and (c) a transfer vector comprising a DNA sequence of interest and lentivirus or HIV cis-acting sequences required for packaging, reverse transcription and integration (see, e.g., page 16, line 5 to page 17, line 5).

Methods for constructing the plasmids and retroviral nucleotide sequences used to produce the packaging cell lines and lentivirus-derived and HIV-derived retroviral particles were readily available in the art at the time the subject application was filed.

The packaging construct provides the codon optimized lentivirus *gagpol* proteins or HIV *gagpol* proteins of the viral particles (see, e.g., page 12, line 22 to page 13, line 13). The envelope encoding plasmid provides a heterologous envelope protein which permits pseudotyping of viral particles generated by the packaging construct (see, e.g., page 14, lines 4-8). The transfer vector provides, *inter alia*, the lentivirus or HIV cis-acting sequences required for packaging, reverse transcription and integration of the viral particles (see, e.g., page 17, lines 12-16).

Thus, armed with the teachings in the specification and what was known to the skilled artisan at the time the subject application was filed, it would have been a routine matter for one skilled in the art to construct packaging cell lines comprising, *inter alia*, a plasmid or retroviral nucleotide sequence which comprises a codon optimized DNA sequence which encodes lentivirus or HIV *gagpol* proteins but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs. Armed with the teachings in the specification and what was known to the skilled artisan at the time the subject application was filed, it would have been a routine matter for one skilled in the art to generate lentivirus-derived or HIV-derived retroviral vector particles having no viral accessory proteins. Accordingly, Applicants submit that the guidance provided in

the specification, coupled with what was known to the skilled artisan at the time the subject application, was filed is sufficient to enable the skilled artisan to make and use the full scope of the claimed method without undue experimentation. No evidence to the contrary has been presented.

The Examiner appears to doubt that the teachings in the specification are sufficient to enable one skilled in the art to practice the claimed invention without undue experimentation because "the prior art teaches that the presence of some sort of transport element, either a Rev/RRE element or CTE, operatively linked to the gagpol coding sequences is essential for formation of recombinant viral particles in a minimal lentiviral system wherein most of the assessory proteins have been omitted." Paper No. 15, at page 6, lines 6-9. The Examiner points to Kim et al. (*J. Virology*, 72(1):811-816 (1998)) as providing evidence in support of his position. Applicants respectfully traverse.

Kim et al. teach a three-plasmid expression system to generate HIV-1-derived retroviral vector particles by transient transfection of mammalian cells. This three-plasmid system features (a) a first plasmid comprising, *inter alia*, HIV sequences for packaging and mRNA export (referred to as a vector genome plasmid); (b) a second plasmid comprising *wildtype* coding sequences for HIV-1 gagpol and coding sequences for RRE or CTE; and (c) a third plasmid comprising the VSV-G gene (envelope protein). Kim et al. teach that their HIV-1-based vector production system lacks *tat*, *vif*, *vpr*, *vpu* and *nef* (Kim et al., page 811, abstract; page 811, column 2, paragraph 2; and page 814, column 2, paragraph 3). Although Kim et al. teach that their HIV-1-based vector production system requires the rev/RRE accessory system (Kim et al., page 814, column 2, paragraph 3), the reference does not question the use of Applicants' three plasmid system which comprises, *inter alia*, a packaging construct comprising a *codon optimized* coding sequence for lentivirus *gagpol* or HIV *gagpol* but not coding sequences for HIV accessory proteins or CTEs, to generate lentivirus-derived or HIV-derived retroviral vector particles having no viral accessory proteins (i.e., without Tat, Vif, Vpr, Vpu, Nef and Rev and RRE). Kim et al. also do not provide evidence that would lead one skilled in the art to the conclusion that Applicants' claimed invention is unbelievable. Accordingly, Kim et al. do not provide a

sufficient basis to question the enablement provided in the subject specification for Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37.

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 have also been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention. More specifically, the Examiner alleges that "[t]here is no support in the specification for the specific limitation of a first nucleotide sequence which comprises a codon-optimized gagpol sequence and, yet, does not comprise coding sequences for any accessory protein or for a constitutive transport element." Paper No. 15, at page 8, lines 7-10. Applicants respectfully disagree with the Examiner's conclusion.

The Examiner appears to be interpreting the phrase "which comprises a codon-optimized HIV or lentiviral gagpol sequence but not coding sequences for HIV or lentiviral accessory proteins or constitutive transport elements" to mean that the packaging vector comprises coding sequences for RRE. However, the specification teaches that lentivirus and HIV accessory proteins include RRE (see, e.g., page 9, lines 19-20; page 10, lines 15-16). Thus, a packaging vector which comprises a codon optimized HIV or lentiviral gagpol sequence but not coding sequences for HIV or lentiviral accessory proteins or constitutive transport elements does not include coding sequences for RRE.

Notwithstanding the above, in an effort to advance prosecution in the subject application, Claims 1, 5, 7, 8, 12, 16, 20, 22, 23, 27, 31 and 35 have been amended to recite that the packaging construct does not comprise coding sequences for RRE. Support for this amendment is found in the specification, for example, at page 9, lines 17-24; page 10, lines 13-20; and page 12, line 22 to page 13, line 2.

Reconsideration and withdrawal of the rejection of Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Twice Amended) A packaging cell line comprising:

a) a mammalian cell;

b) a first retroviral nucleotide sequence in the cell which comprises a codon optimized coding sequence for a HIV *gagpol* but not coding sequences for HIV accessory proteins, Rev response element or constitutive transport elements;

c) a second retroviral nucleotide sequence in the cell which comprises the coding sequence for a heterologous envelope protein; and

d) a third retroviral nucleotide sequence in the cell which comprises a DNA sequence of interest and HIV cis-acting sequences required for packaging, reverse transcription and integration,

wherein said packaging cell line produces a HIV-derived retroviral vector particle.

5. (Twice Amended) A packaging cell line comprising:

a) a mammalian cell;

b) a first retroviral nucleotide sequence in the cell which comprises a codon optimized coding sequence for a HIV *gagpol* but not coding sequences for HIV accessory proteins, Rev response element or constitutive transport elements; and

c) a second retroviral nucleotide sequence in the cell which comprises a DNA sequence of interest and HIV cis-acting sequences required for packaging, reverse transcription and integration.

7. (Twice Amended) A packaging cell line comprising:

a) a mammalian cell;

b) a first retroviral nucleotide sequence in the cell which comprises a codon optimized coding sequence for a HIV *gagpol* but not coding sequences for HIV accessory proteins, Rev response element or constitutive transport elements; and

c) a second retroviral nucleotide sequence in the cell which comprises the coding sequence for a heterologous envelope protein.

8. (Twice Amended) A method of producing a packaging cell line which produces a HIV-derived retroviral vector particle, comprising co-transfecting mammalian host cells with:

a) a first plasmid comprising a codon optimized DNA sequence which encodes HIV *gagpol* proteins but not DNA sequences encoding HIV accessory proteins, Rev response element or constitutive transport elements;

b) a second plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and

c) a third plasmid comprising a DNA sequence of interest and HIV cis-acting sequences required for packaging, reverse transcription and integration,

thereby producing a packaging cell line which produces a HIV-derived retroviral vector particle.

12. (Three Times Amended) A method of producing a HIV-derived retroviral vector particle comprising the steps of:

a) co-transfecting mammalian host cells with:

i) a first plasmid comprising a codon optimized DNA sequence which encodes HIV *gagpol* proteins but not DNA sequences encoding HIV accessory proteins, Rev response element or constitutive transport elements;

ii) a second plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and

iii) a third plasmid comprising a DNA sequence of interest and HIV cis-acting sequences required for packaging, reverse transcription and integration,

b) maintaining the transfected cells under conditions suitable for virus particle production; and

c) recovering virus particle produced in step b).

16. (Twice Amended) A packaging cell line comprising:

a) a mammalian cell;

b) a first retroviral nucleotide sequence in the cell which comprises a codon optimized coding sequence for a lentivirus *gagpol* but not coding sequences for lentivirus accessory proteins, Rev response element or constitutive transport elements;

c) a second retroviral nucleotide sequence in the cell which comprises the coding sequence for a heterologous envelope protein; and

d) a third retroviral nucleotide sequence in the cell which comprises a DNA sequence of interest and lentivirus cis-acting sequences required for packaging, reverse transcription and integration,

wherein said packaging cell line produces a lentivirus-derived retroviral vector particle.

20. (Twice Amended) A packaging cell line comprising:

a) a mammalian cell;

b) a first retroviral nucleotide sequence in the cell which comprises a codon optimized coding sequence for lentivirus *gagpol* but not coding sequences for lentivirus accessory proteins, Rev response element or constitutive transport elements; and

c) a second retroviral nucleotide sequence in the cell which comprises a DNA sequence of interest and lentivirus cis-acting sequences required for packaging, reverse transcription and integration.

22. (Twice Amended) A packaging cell line comprising:

a) a mammalian cell;

b) a first retroviral nucleotide sequence in the cell which comprises a codon optimized coding sequence for lentivirus *gagpol* but not coding sequences for lentivirus accessory proteins, Rev response element or constitutive transport elements; and

c) a second retroviral nucleotide sequence in the cell which comprises the coding sequence for a heterologous envelope protein.

23. (Twice Amended) A method of producing a packaging cell line which produces a lentivirus-derived retroviral vector particle, comprising co-transfecting mammalian host cells with:

a) a first plasmid comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins but not DNA sequences encoding lentivirus accessory proteins, Rev response element or constitutive transport elements;

b) a second plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and

c) a third plasmid comprising a DNA sequence of interest and lentivirus cis-acting sequences required for packaging, reverse transcription and integration,

thereby producing a packaging cell line which produces a lentivirus-derived retroviral vector particle.

27. (Three Times Amended) A method of producing a lentivirus-derived retroviral vector particle comprising the steps of:

a) co-transfecting mammalian host cells with:

i) a first plasmid comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins but not DNA sequences encoding lentivirus accessory proteins, Rev response element or constitutive transport elements;

ii) a second plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and

iii) a third plasmid comprising a DNA sequence of interest and lentivirus cis-acting sequences required for packaging, reverse transcription and integration,

b) maintaining the transfected cells under conditions suitable for virus particle production; and

c) recovering virus particle produced in step b).

31. (Three Times Amended) A HIV-derived retroviral vector particle having no viral accessory proteins produced by the method comprising the steps of:

a) co-transfecting mammalian host cells with:

i) a first plasmid comprising a codon optimized DNA sequence which encodes HIV *gagpol* proteins but not DNA sequences encoding HIV accessory proteins, Rev response element or constitutive transport elements;

ii) a second plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and

iii) a third plasmid comprising a DNA sequence of interest and HIV cis-acting sequences required for packaging, reverse transcription and integration; and

b) maintaining the transfected cells under conditions suitable for virus particle production.

35. (Three Times Amended) A lentivirus-derived retroviral vector particle having no viral accessory proteins, produced by the method comprising the steps of:

a) co-transfecting mammalian host cells with:

i) a first plasmid comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins but not DNA sequences encoding lentivirus accessory proteins, Rev response element or constitutive transport elements;

ii) a second plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and

iii) a third plasmid comprising a DNA sequence of interest and lentivirus cis-acting sequences required for packaging, reverse transcription and integration; and

b) maintaining the transfected cells under conditions suitable for virus particle production.